REMARKS

Claims 5-7, 9-12, and 14-23 are pending. Applicants have amended claim 5 to indicate that the anti-EPO antibodies neutralize the biological activity of EPO. The specification supports this amendment at page 11 and in original claim 8. Thus, this amendment does not add new matter.

Applicants gratefully acknowledge the Office's withdrawal of its previous objections to claims 9, 11, 14-16, 20, 21, and 23; its previous rejection of claims 10, 12, and 22 under 35 U.S.C. § 112, second paragraph; its rejection of claims 17 and 18 under 35 U.S.C. § 102(b) with regard to Sytkowski; its rejection of claims 17, 18, and 20-22 under 35 U.S.C. § 102(b) with regard to Wojchowski and Sytkowski; and its previous rejection of claims 17-21 under 35 U.S.C. § 103(a) with regard to Sytkowski and Kaplan. The Office has also indicated that claims 9, 15, and 16 are allowed.

The Office maintains its rejection of claims 10 and 22 under 35 U.S.C. § 112, first paragraph; claims 5, 6, 11, 12, 14, 17, 20, 23 under 35 U.S.C. § 102(b) with regard to Lin; claims 5-7, 10-12, and 17-23 under 35 U.S.C. § 103(a) with regard to Miyazaki and Lin; and claims 6, 7, 11, and 17-21 for alleged obvious-type double patenting. Applicants address each remaining rejection under its respective statutory section below.

Rejection Under 35 U.S.C. § 112

The Office continues to reject claims 10 and 22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to indicate that the inventors had possession of the invention at the time of filing. Specifically, the Office notes that these claims recite EPO

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derivatives. According to the Office, however, the specification mentions but does not teach EPO derivatives, define EPO derivatives, or provide any examples of EPO derivatives. Applicants previously explained that Example 7 in the specification describes the purification of EPO muteins by affinity chromatography. In addition, the specification also describes EPO muteins as modified EPO molecules and further instructs that antibodies to these muteins may be generated.

The Office now responds by asserting that the genus of EPO derivatives encompasses species with widely varying attributes (i.e., truncation mutants, splice variants, etc.). According to the Office, adequate written description requires more than just a reference to the genus due to the alleged variability of the species involved. In addition, the Office interprets the term "muteins" to be a subset of the term "derivatives" and thus discounts the specification's description of muteins at page 7, lines 2-8. Because the specification allegedly does not provide any examples of EPO derivatives and the term "derivatives" allegedly encompasses a group of molecules with varying characteristics, the Office concludes that the specification does not meet the written description requirement for claims 10 and 22. Applicants respectfully traverse on several grounds.

First, the Office's interpretation of the specification, that the term "derivatives" is broader than the term "muteins" contradicts the specification's teaching. At page 7, the specification teaches that muteins can be modified. The term "modified" in that context would be understood by the skilled artisan to cover the same types of modifications that are associated with derivatives of a protein. Thus, the terms are equivalent and should be interpreted to include all possible protein modifications. The Office believes that the

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specification does not "provide any examples of EPO derivatives." Paper 27 at page 2. The specification, at page 7, clearly provides one example of a modification that could be found in an EPO derivative or mutein: EPO proteins that have a change in their primary amino acid sequence.

Second, *arguendo*, even if the terms "derivative" and "mutein" did not have equivalent meanings, as the Office suggests, the specification still clearly contemplates the invention of claims 10 and 22. The specification, at page 6, lines 23-26 expressly indicates that "anti-EPO antibodies according to the invention are used for purifying EPO, EPO derivatives, or EPO peptides." When considering whether the specification meets the written description requirement, the U.S. Court of Appeals for the Federal Circuit has noted that exact, *ipsis verbis* support need not be present. *See In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

In this case, the specification need not list every single possible protein derivative encompassed by the claims. Rather, the question becomes whether a skilled artisan, given the specification's teaching and what was known in the art at the time of filing, would conclude that the inventors were in possession of the invention. The specification clearly teaches that anti-EPO antibodies can be used to purify EPO derivatives. A skilled artisan, at the time of filing, would understand the term "derivatives" to cover changes in the EPO protein such as changes in amino acid sequence or changes in the glycosylation of the protein. The Office itself has demonstrated that a skilled artisan would understand the term "derivatives" to include various modifications to the EPO protein. Specifically, at page 2, fourth paragraph, the

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Office lists additional alternatives such as denatured EPO, truncations, and splice variants.

Finally, Applicants note that claims 10 and 22 are not composition claims that target the EPO derivatives themselves. Rather, these claims recite a method of using an anti-EPO antibody to purify EPO, an EPO derivative, or an EPO peptide and a method of purifying EPO, an EPO derivative, or an EPO peptide. The specification contains ample discussion of preparing such antibodies and using them in the context of chromatography to purify EPO or EPO muteins. *See* pp. 10-11 and Example 7.

For the reasons set forth above, Applicants respectfully request that the Office withdraw its rejection of claims 10 and 22 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 102

Claims 5, 6, 11, 12, 14, 17, 18, 20, 21, and 23 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lin (U.S. Patent 4,703, 008; "Lin"). There are three major aspects to the Office's rejection. First, the Office believes that Lin's antibodies inherently have neutralizing activity. Second, the Office also believes that Applicants have the initial burden to prove that the method of Lin does not anticipate the claims of the instant invention. Finally, the Office continues to dismiss Applicants' observation that Lin expressly reports that the 144-166 peptide fails to show EPO activity. Applicants traverse each of these contentions as set forth below.

Neutralizing Activity: Solely to clarify the invention and facilitate prosecution, Applicants have amended claim 5 to indicate that the anti-EPO antibodies neutralize the biological activity of EPO. The Office acknowledges that Lin does not teach that the antibodies generated by their peptide are neutralizing. *See* paper 27 at page 5. But the

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Office argues that "it would be inherent in the anti-144-166 antibodies that a subset of antibodies would be neutralizing as the instant specification is claiming that anti-152-166 antibodies are neutralizing." Id. The Office implicitly assumes that the epitopes in the 152-166 peptide will remain unchanged even in the context of Lin's additional amino acid sequence.

The Office now attempts to support its assertion by describing how B cells can be stimulated to produce antibodies. *See* paper 27 at pp. 7 and 8. The Office describes a subset of antigens, thymus-dependent antigens, for which T cells must be involved in order to facilitate B cell activation. In essence, the B cell binds to the antigen, ingests it, and presents epitopes to helper T cells which in turn cross-stimulate the presenting B cell. The Office omits the alternate description of how B cells may be activated in which helper T cells are not involved. With thymus-independent antigens, the antigen itself is responsible for B cell activation. Whether an antigen is a thymus-dependent antigen or a thymus-independent antigen, the initial step requires that the antigen bind to the antibody molecules on the B cell surface, making the conformation of the peptide important. The Office's statement that conformation is not important due to antigen processing in the B cell is inaccurate, as antigen processing in that context serves to stimulate T cells to then allow for further B cell response to the antigen already bound to the B cell. *See generally* Charles A. Janeway, Jr. & Paul Travers, *Immunobiology: The Immune System in Health and Disease* (Miranda Robertson ed., Garland Publishing 1994).

Lin's 144-166 peptide is clearly not identical to the 152-166 peptide. In general, antibodies are better adapted to respond to three-dimensional (discontinuous) epitopes,

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while T cells normally address linear epitopes. *See Id.* If the antibodies recognize a three dimensional structure in the 152-166 peptide, addition of extra amino acids as in Lin's peptide could certainly change that structure and alter the epitopes responded to by naïve B cells. Regarding the Office's discussion of antigen processing, as discussed above, Lin's additional amino acids may change that processing and in turn alter the T cell stimulation needed for thymus-dependent antigens. Moreover, the somatic mutation involved in B cell maturation is part of a process called affinity maturation, which selects for antibodies that have a high affinity to the *epitopes*. Applicant argues that the additional sequence in Lin's peptide (about 50%) would more likely than not change the peptide's epitopes to which any affinity maturation would be directed. At a minimum, such conjecture cannot support a rejection based on inherency.

Applicants emphasize that the Office is relying on the Doctrine of Inherency to assert its rejection of claims 5, 6, 11, 12, 14, 17, 18, 20, 21, and 23. The bar of proof for inherency is quite high. The Office and the Court of Appeals for the Federal Circuit have found that "in order for a claim to be inherent in the prior art it is not sufficient that a person following the disclosure sometimes obtain the result set forth in the claim, it must invariably happen." *Glaxo, Inc. v. Novopharm Ltd.*, 830 F.Supp. 871, 874, 29 USPQ2d 1126, 1128 (E.D.N.C. 1993), *aff'd,* 52 F.3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995). In other words, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. §2112 (8th ed. 2001) (emphasis in the original) (*citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)). Instead, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive

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matter is necessarily present in the thing described, and that it would be so recognized by persons of ordinary skill.'" *Id. (citing In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). Thus, the mere existence of alternative peptide conformation and T cell activation demonstrates that the Lin's antibodies do not necessarily or invariably have neutralizing activity. Applicants also note that the Office indirectly acknowledges this by continuing to assert that its conclusions about the alleged neutralizing activity of Lin's antibodies are "reasonable." Paper 27, at page 6, second full paragraph. Neither reasonableness nor probability are the standard for inherency.

Improper Shifting of the Burden of Proof: The Office asserts that Applicants bear the burden to prove that Lin does not anticipate the claimed invention. *See* paper 27 at pages 6 and 8. The Office relied on MPEP § 2111.03 for this assertion, which refers to the situation where the Examiner has established a *prima facie* case of anticipation. As discussed above, the Office has not met its initial burden of establishing a *prima facie* case of anticipation because the use of the Doctrine of Inherency to fill in the missing element of neutralization is improper.

Lin's peptide fails to show *in vivo* EPO activity: In independent claims 17 and 20, the recited antibody is "directed against epitopes that bind to the EPO receptor." Applicants previously noted that Lin reported no *in vivo* EPO activity with the 144-166 peptide. The Office continues to dismiss this observation and assert possible alternate reasons as to why an EPO epitope may bind the EPOR and not exhibit EPO activity. Applicants noted that the Office used common sense to compensate for the fact that Lin reported no *in vivo* EPO activity with the 144-166 peptide. The Office now replies that it

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used common sense only to respond to Applicants' arguments and that this aspect of the Office Action was not essential to the rejection of the pending claims. Applicants respectfully submit that the Office provided these arguments to defend its rejection of the claims, making these common sense arguments an essential part of the rejection and therefore improper.

Moreover, the Office also contends that "antibodies raised to the 152-166 peptide directly binds to the EPO receptor." Page 7, lines 5-6. This is a complete mischaracterization of the invention of claims 17 and 20. These claims state that the antibodies bind to epitopes that bind to the EPOR. The antibodies of these claims do not bind the EPOR directly, but bind to that part of EPO that binds to the EPOR. Thus, this aspect of the Office's argument is irrelevant to the claims.

Assessing a peptide's *in vivo* activity would be accepted by an person of ordinary skill in the art as an indirect indicator of binding to the EPOR. As such, it is an indirect way of addressing claim 17's requirement that the "anti-erythropoietin (EPO) antibody [is] directed against epitopes that bind to the EPO receptor." It is the Office's burden to establish a *prima facie* case of anticipation. The proposed alternate explanations as to why Lin lacks *in vivo* activity do not change the fact that Lin's peptide did not give any *in vivo* EPO activity, even when used with other peptides.

As discussed above, Lin cannot anticipate claims 5, 6, 11, 12, 14, 17, 18, 20, 21, and 23 because Lin does not contain every element of these claims. Applicants request that the Office withdraw its rejection.

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Rejections Under 35 U.S.C. § 103

The Office continues to reject claims 5-7, 10-12, 14, and 17-23 under 35 U.S.C. § 103(a) as allegedly obvious over Miyazaki et al. (*J. Immunol. Meth.* 113:261-67 (1988); "Miyazaki") in view of Lin. Briefly, the Office believes that Lin teaches the embodiments of claims 5, 6, 11, 12, 14, 17, 18, 20, 21, and 23 but does not teach a method in which the 144-166 peptide may be used to generate monoclonal antibodies ("MAbs") useful for affinity purification of EPO. Thus, it uses Miyazaki to target claims 7, 10, and 19 by contending that this reference allegedly teaches MAbs against human EPO and immunoaffinity columns comprising these MAbs. The Office concludes that it would be obvious to substitute Lin's 144-166 peptide into Miyazaki's method and would have been motivated to do so because of Miyazaki's alleged teaching on the superiority of affinity columns based on MAbs.

As Applicants noted in the prior response, Miyazaki teaches away from the invention of these claims. Regarding the neutralizing activity of the antibody of claims 5-7, 10-12, 14, and 23, Miyazaki expressly reports that none of their MAbs neutralized EPO activity. *See* page 266. As to the requirement that the antibody of claims 17-23 is directed against epitopes that bind to the EPOR, Miyazaki concluded that these MAbs do not bind to the active site of EPO, i.e., the region that binds to the EPOR. *See Id.* In the current Office Action, the Office has not addressed these clear contrary teachings in Miyazaki. Instead, the Office simply maintains that Lin does teach the antibodies of the invention. As discussed above, the Office's rejection of 5, 6, 11, 12, 14, 17, 20, and 23 as anticipated by Lin is incorrect.

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The Office believes that that it would be obvious to substitute Lin's 144-166 peptide into Miyazaki's method and that the skilled artisan would have been motivated to do so because of Miyazaki's alleged teaching on the superiority of affinity columns based on MAbs. Applicants address each reference so as to demonstrate what the references, as a whole, do not teach. *Arguendo*, even if the Office were correct, and Lin did teach the invention's antibodies and Miyazaki taught that affinity columns based on MAbs were superior to other columns, neither reference provides the motivation for the invention itself. Lin does not teach affinity columns nor production of MAbs. Thus, there is no motivation to use Lin's antibodies for such pursuits. As Applicants have noted previously, the Office cannot apply its own knowledge of the art or "common sense" to supply motivation. Motivation must be present in the references used to make the rejection.

Regarding Miyazaki, even if this reference teaches that affinity columns based on MAbs are superior, the antibodies that Miyazaki used are clearly not the antibodies contemplated by the rejected claims. A general observation that MAb affinity columns may work well cannot provide the skilled artisan with the specific motivation to make a specific affinity column using neutralizing antibodies. Moreover, Miyazaki's antibodies were not neutralizing and did not target epitopes that bind the EPOR. Thus, this reference at best teaches affinity columns using non-neutralizing, non-EPOR epitope directed MAbs. The skilled artisan, based on Lin's teaching and Miyazaki's teaching, taken alone or together, could not find the requisite motivation to make the invention of claims 5-7, 10-12, 14, and 17-23. Applicants therefore request that the Office withdraw its rejection.

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Obvious Type Double Patenting

Claims 6, 7, 11, and 17-21 remain rejected based on obvious type double patenting in light of U.S. Patent 5,712,370. Applicants request that the Office continue to hold this rejection in abeyance until all patentable subject matter in this application has been determined. In requesting abeyance, Applicants have not expressed an intention to file a Terminal Disclaimer. Rather, this rejection will be refuted or a Terminal Disclaimer will be filed once Applicants consider this rejection in light of all the allowable subject matter.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of pending claims 5-7, 9-12, and 14-23.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 11, 2004

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